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# ASSESSMENT OF METHYLPHENIDATE SENSITIZATION USING A TWO-LEVER DRUG DISCRIMINATION PROCEDURE

by

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A Thesis
Submitted to the
Faculty of The Graduate College
in partial fulfillment of the
requirements for the
Degree of Masters of Arts
Department of Psychology

Western Michigan University
Kalamazoo, Michigan
June 2000

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ACKNOWLEDGMENTS

I would like to express my gratitude to the members of my graduate committee for taking the time to review my work. Sincere thanks go to my faculty advisor, Dr. Lisa Baker, who generously donated her time and expertise to this project and also to Dr. Scott H. Kollins for his collaboration that was so crucial to the success of this project. Special thanks are also due to my undergraduate assistant, Danielle Larson, her enthusiasm and dedication to the research contained in this thesis was phenomenal.

I would also like to express my appreciation to everyone in the Behavioral Neuropharmacology Laboratory for the support and advice provided throughout this project. Finally, to my family, thanks for your continuing support and encouragement .

Ann Marie Heidema

# ASSESSMENT OF METHYLPHENIDATE SENSITIZATION USING A TWO-LEVER DRUG DISCRIMINATION PROCEDURE

Ann Marie Heidema, M.A.

Western Michigan University, 2000

The current study examined the effects of methylphenidate (MP) pre-exposure on the acquisition of cocaine discrimination in rats. Sixteen male Sprague-Dawley rats were administered either 10 mg/kg MP or saline for five consecutive days. Following this pre-treatment phase, animals were trained to discriminate 10 mg/kg cocaine-hydrochloride from saline using a two-lever fixed-ratio 20 (FR20) schedule of food reinforcement. Acquisition of cocaine discrimination, as indicated by the number of sessions to criterion, did not differ significantly between the two-pre-treatment groups (MP = 35.5 ± 2.4; SAL = 31.6 ± 2.3). Stimulus generalization tests were conducted with cocaine and methylphenidate using cumulative dosing procedures. The dose response curves for both methylphenidate and cocaine were not significantly different between the two pretreatment groups. Methylphenidate completely substituted for cocaine at doses of 4.0 mg/kg and 8.0 mg/kg in both treatment groups.

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# INTRODUCTION

## The Relationship Between ADHD and SUD

The relationship between Attention-deficit hyperactivity disorder (ADHD) and substance use disorder (SUD) is a multi-faceted dilemma that has been discussed extensively in the literature. Studies have shown the co-occurrence of ADHD and SUD to be larger than would be expected by chance (Biderman, Wilens, Mick, Milberger, Spencer, and Faraone, 1995; Levins and Kluber, 1995). Several studies indicate that ADHD subjects have a significantly higher lifetime rate of drug and alcohol abuse or dependence when compared to non-ADHD controlds (Biederman, 1995). Schubiner, Tzelepis, Isaacson, Warbasse, Zacharak, and Musiel (1995) found an increased incidence of ADHD in populations of alcoholics and other drug abusers. There are multiple factors that contribute to this relationship, including variations in assessments, diagnostic criteria, and the reliability of the report. One hypothesis regarding the significant co-occurrence of ADHD and SUD is a self-medication hypothesis.

This hypothesis postulates that individuals use psychoactive substances in an attempt to minimize the experience of psychiatric symptoms. The rationale is that since cocaine abusers have a high incidence of co-morbid SUD and ADHD, they may abuse cocaine as a way of self- medicating. Further evidence to support this hypothesis is that cocaine has pharmacological actions that are similar to those of methylphenidate (MP)

(Levin and Kluber, 1995; Volkow, Ding, Fowler, Wang, Logan, Gatley, Dewey, Ashby, Liebermann, Hitzemann, and Wolf, 1995). Recent studies confirm that individuals with ADHD symptoms persisting into adulthood are at greater risk for having a substance use disorder. Levin and Kluber (1995) found that 35% of cocaine abusers seeking treatment had a history of childhood ADHD and approximately 15% of cocaine abusers seeking treatment may have adult ADHD. Sustained-release methylphenidate in daily doses up to 80 mg, have been successful in reducing symptoms such as cocaine craving, and cocaine use among cocaine abusers with ADHD (Levin, Evans, McDowell, and Kleber, 1998; Grabowski, Roache, Schmitz, Rhoades, Creson, and Korszun 1996). However, further investigation is needed to support the use of MP for reducing cocaine dependence.

In efforts to delineate the relationship between stimulant use and abuse, Biderman, Wilens, Mick, Spencer, and Faraone (1999) address the risk for SUD associated with previous exposure to psychotropic medication in a longitudinal study of boys with ADHD. They found unmedicated subjects with ADHD were at a significantly increased risk for SUD when compared with non-ADHD controls, as well as with medicated ADHD subjects.

Still the idea that pharmacotherapy increases the risk for SUD persists in diagnostic literature and in the popular press (Altman, Everitt, Glautier, Markou, Nutt, Oretti, Phillips, and Robbins, 1996). Although clinical investigations show stimulant medication to be particularly effective in treating the behavioral aspects of ADHD, controversy surrounding the use of stimulant medication in the treatment of children endures. Currently an estimated 1.29 million children are being treated with psychostimulants

(Julien, 1997). In 90% of diagnosed ADHD cases the prescribed treatment is methylphenidate hydrochloride (Julien, 1997; Goldman, Genel, Benzman, & Slanetz, 1998). Although this treatment is effective, there is concern regarding the pharmacological treatment of children with a stimulant that possesses commonalties with drugs of abuse such as cocaine and d-amphetamine. Although MP is self-administered by animals (Neilsen, Duda, Mokler, & Moore, 1984; Risner & Jones, 1976; Johanson & Schuster; 1975) and is reportedly abused by humans (Fulton & Yates, 1988; Dakis & Gold, 1990; Haglund & Howerton, 1982) more research is required to elucidate the effects of methylphenidate treatment in subjective experience of stimulants.

## Sensitization to Drug Effects

Sensitization is a progressive increase in a drug effect with repeated administration or rather a persistent hypersensitivity to an effect of the drug as a consequence of past history. Sensitization is operationally defined as a shift in a dose-effect function to the left following repeated drug administration. The repeated administration of psychoactive compounds often results in modification of the subject's behavioral responses, frequently making the organism more sensitive to the effects of the drug. Schenk and Partridge (1997) reviewed the literature on the effects of stimulant pre-exposure on self-administration and found reports that repeated exposure to stimulants sensitizes subjects to the reinforcing properties of subsequent exposures. However, Schenk and Partridge (1997) also found reports that repeated exposure produces tolerance to the reinforcing effects of subsequent exposures. Tolerance can be described as a shift in the dose effect function to

the right, illustrating that higher doses are required to produce the same effect. Extended daily self-administration of cocaine produces tolerance to the reinforcing effects of cocaine in rats, however, intermediate drug exposure has been shown to produce sensitization to the reinforcing effects of cocaine in a variety of behavioral assays ( Altman, et al., 1996).

Yet there is much debate surrounding the topic of sensitization due to difficulties inherent in replication of the phenomenon. This may be due to the fact that only certain treatment regimens are effective. There are numerous methodological factors to consider, such as the drug used, dose, time course, route, and behavioral measures. Unfortunately, there has been little systematic research on the specific parameters required to produce the desired result. There is also debate regarding the use of appropriate behavioral measures for sensitization. Robinson and Berridge (1993) argue that measures of locomotion are often not good indicators of a profound sensitization phenomenon, because stimulant-induced locomotion does not produce a strictly linear dose-effect function.

The majority of previous studies have examined the effects of sensitization using the behavioral measures of locomotion or self-administration. Repeated administration of stimulants (i.e. amphetamine, meth-amphetamine, methylphenidate and caffeine) produces long-lasting behavioral effects (Gayton, al-Rahim, Swann, and Dafny, 1997; Horgan, Giles, and Schenk, 1990; Kolta, Shreve, and Uretsky, 1985). There is evidence that sensitizing regimens, enhance the acquisition of drug taking behavior in rats (Valdez and Schenk, 1994; Horger, Shelton, and Schenk, 1990; Schenk, Worley, McNamara, and Valadez, 1996). For example, Valadez and Schenk

assessed the effects of amphetamine (2.0 mg/kg, i.p., for 9 consecutive days) pre-exposure on the subsequent reinforcing effects of cocaine and found that latency to acquire reliable cocaine self-administration was shorter in the amphetamine pre-exposed animals than in the saline pre-exposed subjects. They also noted the sensitizing effects of amphetamine exposure persisted for 45 days following the treatment

Furthermore, sensitization has also shown to influence locomotor behavior. McNamara, Davidson, and Schenk (1993) examined a comparison of the locomotor-activating effects of acute and chronic exposure to methylphenidate or amphetamine. They reported that acute exposure to methylphenidate (5.0, 10.0, or 20.0 mg/kg) and amphetamine (0.5, 1.0, 2.0, and 4.0 mg/kg) produced a dose-dependent increase in horizontal activity with cocaine reinstatement (McNamara et al., 1993). The 20.0 mg/kg methylphenidate group exhibited smaller increases in activity with repeated doses; the authors' state that this may suggest chronic exposure produces tolerance. In another study, MP sensitization (2.5 mg/kg, for five consecutive days) produced augmented locomotor effects to challenge doses of MP (0.6 and 2.5 mg/kg) (Gayton, Sahim, Swarm, and Dafny, 1997). Kolta, Shreve, and Uretsky (1985) found that after rats were chronically pretreated with MP (20 mg/kg, i.p., for five consecutive days) the stereotypical behavioral response to challenge doses of amphetamine was significantly enhanced.

The contention that early exposure to stimulants may be associated with potential for abuse has not yet been fully examined. Given the growing population of children with ADHD currently receiving psychomotor stimulants, further study of stimulant exposure as a factor for SUD risk is

required. Although the drug effects may be dependent on the clinical regime of treatment, the potential for stimulant sensitization poses an interesting question regarding risk for SUD. A clinically relevant experiment conducted by Brandon, Marinelli, & White (1999) recently examined the effects of cross-sensitization to cocaine following repeated methylphenidate exposure in juvenile rats. They found MP pre-exposure (10 mg/kg, i.p. for seven consecutive days) significantly enhanced the acute effects of cocaine on locomotor and rearing behaviors.

Previous drug exposure can have profound effects on behavior, enhancing not only the reinforcing effects of drugs as illustrated by non-human self-administration, but also by the behavioral activating effects of drug reinstatement as illustrated in the by the locomotor studies. However, the question of how previous exposure to stimulants affect the subjective experience remains. The reinforcing subjective effects of drugs as measured by self-report in humans, correlates with abuse potential of that drug. Development of a model that addresses the issue of drug history and subjective drug experience may have serious implications for clinical populations.

## The Drug Discrimination Procedure

Drug discrimination is a common model for evaluating the 'subjective' effects of drugs. Discriminative stimulus effects of drugs are the properties of drugs, which act as cues directing behavior. The correlation between patterns of cross-generalization in non-human drug discrimination experiments and similarities in subjective effects in human subjects serve as powerful evidence

to support this theory (Altman et al, 1996; Stolerman, 1993). This work is distinguished from other branches of behavioral pharmacology because it is not based on observations of how drugs influence an ongoing baseline of behavior that is stabilized in the absence of drug. In this model, drugs serve as stimuli. Discriminative stimulus effects of drugs in non-humans refer to the capacity of animals to use drug (or placebo) states as discriminative cues to respond to reinforcement. Discriminative stimulus effects may enhance our understanding of drug dependence, for it is widely accepted that the subjective effects of drugs contribute to the extent to which they are abused.

Relatively few studies directly address the role of previous drug history as a determination of discriminative response. In a study conducted by Ator and Giffiths (1993), previous drug history was found to affect the dose response curve in generalization tests. History of self-administration of the benzodiazepine, midazolam, in baboons produced a shift to the left in generalization tests when compared to curves generated before self-administration training, illustrating an enhanced drug sensitivity to low doses following exposure. The data suggest that sensitivity to the discriminative stimulus effects of a drug can be modulated by previous experience with that drug. This study was essential in expanding understanding of the drug history on stimulus properties. However, this study was conducted with only two subjects, and was subject to procedural interaction between discrimination and self-administration assays. This study illustrates the importance of investigating the effects of drug history on dose response functions.

## The Purpose of the Present Study

The primary goal of the present study was to assess the role of methylphenidate exposure in the discriminative stimulus properties of cocaine. The effects of pretreatment with methylphenidate on acquisition of cocaine discrimination, terminal accuracy across training sessions, latency to the first fixed ratio (FR), and generalization testing with both cocaine and methylphenidate were examined.

A secondary goal of this study was to examine the usefulness of the drug discrimination assay as a tool for studying sensitization. Implications for the clinical relevance of methylphenidate exposure to cocaine sensitivity are also discussed.

# METHODS

## Subjects

Sixteen male Sasco Sprague-Dawley rats (Charles River Breeding Colony, Portage, MI) approximately five weeks old at the beginning of the study were used as subjects. The animals were individually housed in acrylic cages with celludry bedding, in a colony maintained on a 12 hour light/dark cycle (0700 to 1900) and at a relatively constant temperature (20-22 ° C) and humidity (50-65%). Water was provided in the home cages ad libitum, and food was restricted to maintain the animals at 85% of their free-feeding body weights. The animals were maintained in accordance with the general principles of animal husbandry outlined by the National Institutes of Health and the experimental protocol was reviewed and approved by the Institutional Animal Care and Use Committee of Western Michigan University (see Appendix A).

## Apparatus

Training and test sessions were conducted in eight standard operant chambers (MED Associates Inc., Georgia, VT), housed in sound and light attenuating shells, which provide ventilation and masking noise. The experimental chambers were equipped with an overhead house light, a food pellet dispenser and three retractable levers. MED-PC for windows (MED Associates Inc., Georgia, VT) instrumentation and software were used to control the experimental events and data collection. Dustless precision 45 mg pellets (Bioserv, Frenchtown, NJ) severed as the food reinforcement.

## Drugs

Methylphenidate-hydrochloride was administered intraperitoneally at a dose of 10 mg/kg to eight rats during a pre-exposure period (see below). A dose of 10 mg/kg cocaine was used during discrimination training. Doses were calculated based on the salt. The drug was dissolved in sterile 0.90% saline and injected intraperitoneally. Drugs were obtained from the National Institute of Drug Abuse (NIDA, Bethesda, MD).

## Training Procedures

### Lever Press Training

Animals were auto-shaped to lever press on the center lever for food reinforcement prior to any drug exposure. In the first session, no levers were present, and food was delivered on a fixed time 60-sec interval (FT 60) schedule for two 35 minute sessions, to pair the sound of the pellet drop with food delivery. The center lever was then presented and lever presses were reinforced on a continuous reinforcement schedule for a 20 minute period. Following acquisition of the lever pressing response, 20 minute training sessions were conducted where lever pressing was reinforced on a fixed ratio (FR) schedule that gradually incremented from a FR 1 to a FR 20, until responding was stable on the FR 20 resetting schedule.

### Methylphenidate Exposure

Once lever pressing behavior was acquired and responding was

maintained on a FR 20 schedule of food reinforcement, the animals were randomly assigned to one of two groups. Control for high and low responding rates were taken into account. Subjects with rates of greater than .50 responses per second were deemed high responders and subjects with rates of less than .50 responses per second were deemed low responders. High and low responders were equally distributed to each of two treatment groups. One group of eight rats received an intraperitoneal (i.p.) injection of MP (10mg/kg) and one group of eight rats received saline injections once per day for five consecutive days in their home cage (Brandon, Marinelli, and White, 1999).

Discrimination Training

Following the pre-exposure procedure, discrimination training began. Fifteen minutes prior to the onset of each training session, the rats were administered a single intraperitoneal (i.p.) injection of cocaine (10 mg/kg) or saline. Animals received an average of three drug injections per week, with no more than two consecutive days of drug injections. Drug or saline conditions were presented in a semi-random order, such that neither condition was presented for more than two consecutive sessions. Drug discrimination training involved a two-lever operant task under a fixed ratio 20 (FR20) schedule of food pellet delivery. Twenty-minute training sessions were conducted five - six days per week at approximately the same time each day (8:00 am -10:00 am). The criterion for discrimination was set at a minimum of 80% correct lever responses before the first reinforcer of each training session for at least nine out of ten consecutive training sessions.

Dose Response Tests

Cumulative dosing procedures were employed to confirm accurate stimulus control. Once this criterion was met by the subjects, cumulative dose response tests were administered with cocaine (0, 0.3, 1.0, 3.0, 10.0 mg/kg). Animals were administered the first injection (0 mg/kg) and after a 10 minute period they were placed in the operant chambers until the animal made 20 consecutive responses or five minutes had expired. 20 consecutive responses on either lever produced one 45 mg pellet food reinforcer. The animals were then removed from the test chambers and administered a second dose (0.30 mg/kg). Following another 10 minute period, they were again placed into the testing chamber for a five minute period. This procedure was repeated with the third, fourth, and fifth doses (cumulatively equaling 10.0 mg/kg). This dosing procedure was administered on two separate occasions, once following a drug training day and once following a saline training day. In addition, a stimulus generalization test was administered with MP (1.0-8.0 mg/kg). Half of the subjects were tested following a cocaine training day, and half of the subjects were tested after a saline training day. Training sessions were conducted on the days between tests.

## Data Analysis

The number of sessions to criterion was calculated and a between-group comparison was made. Data obtained from, two subjects (one saline pretreated, and one MP pretreated) were not included in the analysis due to

the requirement for individually tailored discrimination training that was not consistent with the other subjects. Analysis of the percent correct during the first FR and the percentage of total responses on the drug appropriate lever across training sessions were compared between groups and a linear regression analysis was conducted on the slope and elevation. A between group analysis of latency to complete the first FR was also conducted.

Cumulative dosing procedures with reinforced trials were used for dose response tests. Test data from animals that did not complete the FR 20 requirement were not included in the data analysis of testing sessions. Two way ANOVAs (group X dose) were conducted on results from each dose-response test. Dose response data were presented as the percent of total responses made on the drug-appropriate lever during test sessions. 80% or greater drug lever selection was considered evidence for stimulus generalization. Response rate was presented as the number of responses made on either lever per second during test sessions. For each dose tested, the mean and the standard error of the mean were calculated. Two way ANOVAs (group X dose) were conducted on each set of dose response data. Statistical analysis were conducted using the software GraphPad Prism (Version 2.0; GraphPad, Inc., San Diego, CA).

# RESULTS

Fourteen of the sixteen subjects readily acquired the discrimination (minimum of 80% condition-appropriate responses prior to the delivery of the first reinforcer in at least nine of ten consecutive training sessions) in the present experiment. One subject in each group required tailored discrimination training. Surprisingly, pre-exposure to methylphenidate did not appear to facilitate acquisition of the discrimination. In fact, the number of sessions to criterion was slightly increased in the MP pretreated subjects compared to the saline pretreated subjects. A t-test on the number of sessions to criterion was not statistically significant between the two groups ($t=1.142$, $df_{12}$, $p=0.28$). The mean of the MP pretreated group was $35.4 \pm 2.4$ (Range: 26-47, n=7), and the mean of the control group was $31.6 \pm 2.3$ (Range: 26-44, n=7). The results are displayed in Figure 1.

The measure of terminal accuracy for the percent correct lever choice for the first fixed ratio illustrates considerable variability over the 69 training sessions in both treatment groups. The total percent correct over training sessions is also highly variable (Figure 2). This is also evident by examining the individual subject variability plotted for both the MP pretreated group and the saline pretreated group in Figures 3 and 4, respectively.

Visual analysis of the terminal accuracy data suggested that the MP pretreated group might have a significantly lower accuracy over sessions. Examination of the mean percent correct across sessions in which subjects

responded below the established 80% drug appropriate lever criterion was calculated for each group; the means were collapsed over sessions. The mean for the MP pretreated group was 44.45 ± 3.5 (n=64, sessions below 80%) and mean for the saline pretreated group was 45.49 ± 3.6 (n = 53, sessions below 80%). The difference between groups was not statistically significant, according to a t-test on between groups number of sessions below criterion (80%) (t= 0.206, $df_{115}$, p 837).

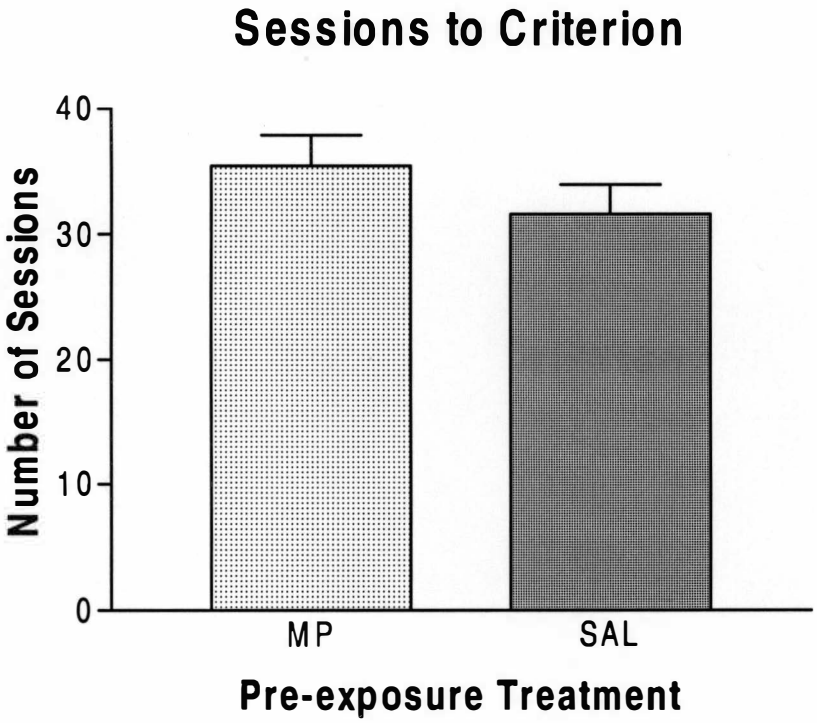


Figure 1. Sessions to Criterion for Cocaine Discrimination.

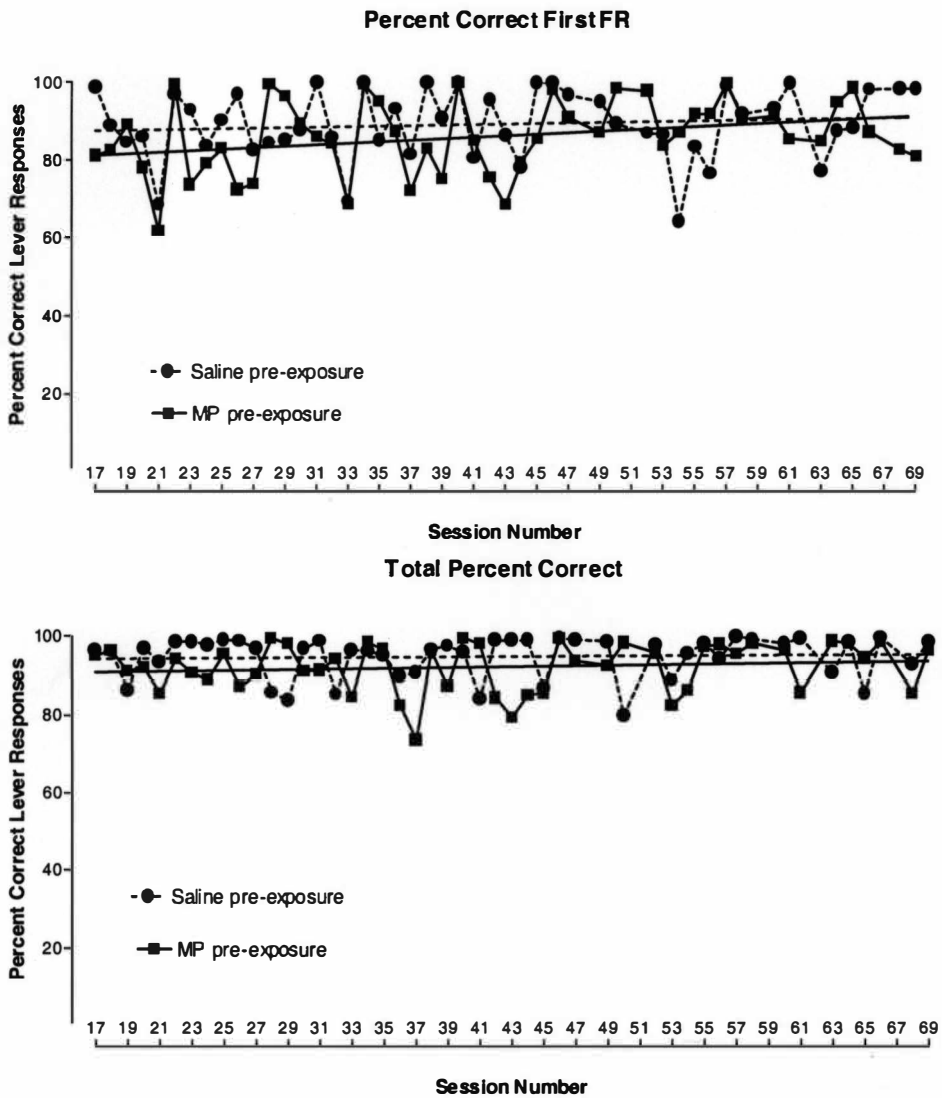


Figure 2. Terminal Accuracy on Percent Correct First FR and Total Percent Correct across Training Sessions.

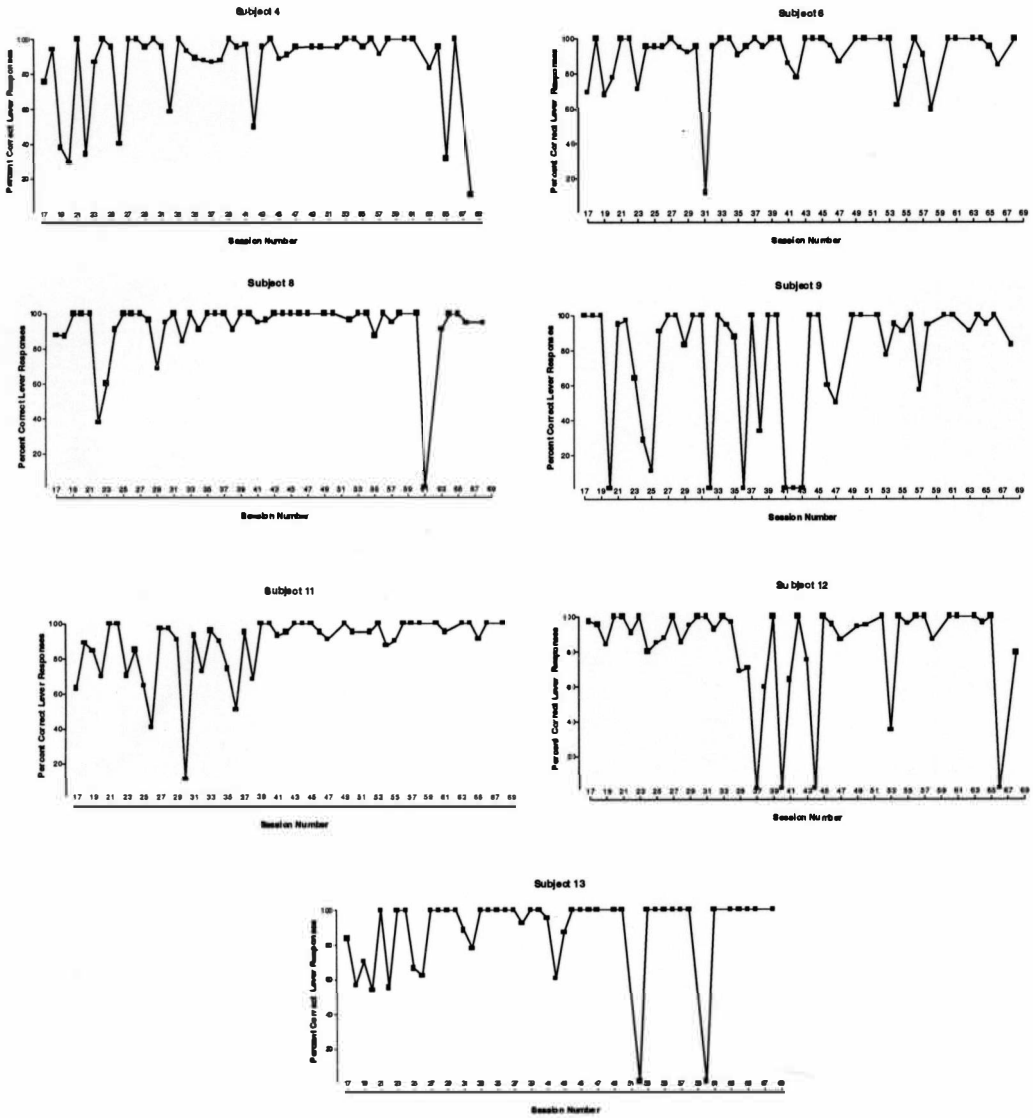


Figure 3. Individual Subject Data for Percent First FR Across Training Sessions for the MP Pretreated Group.

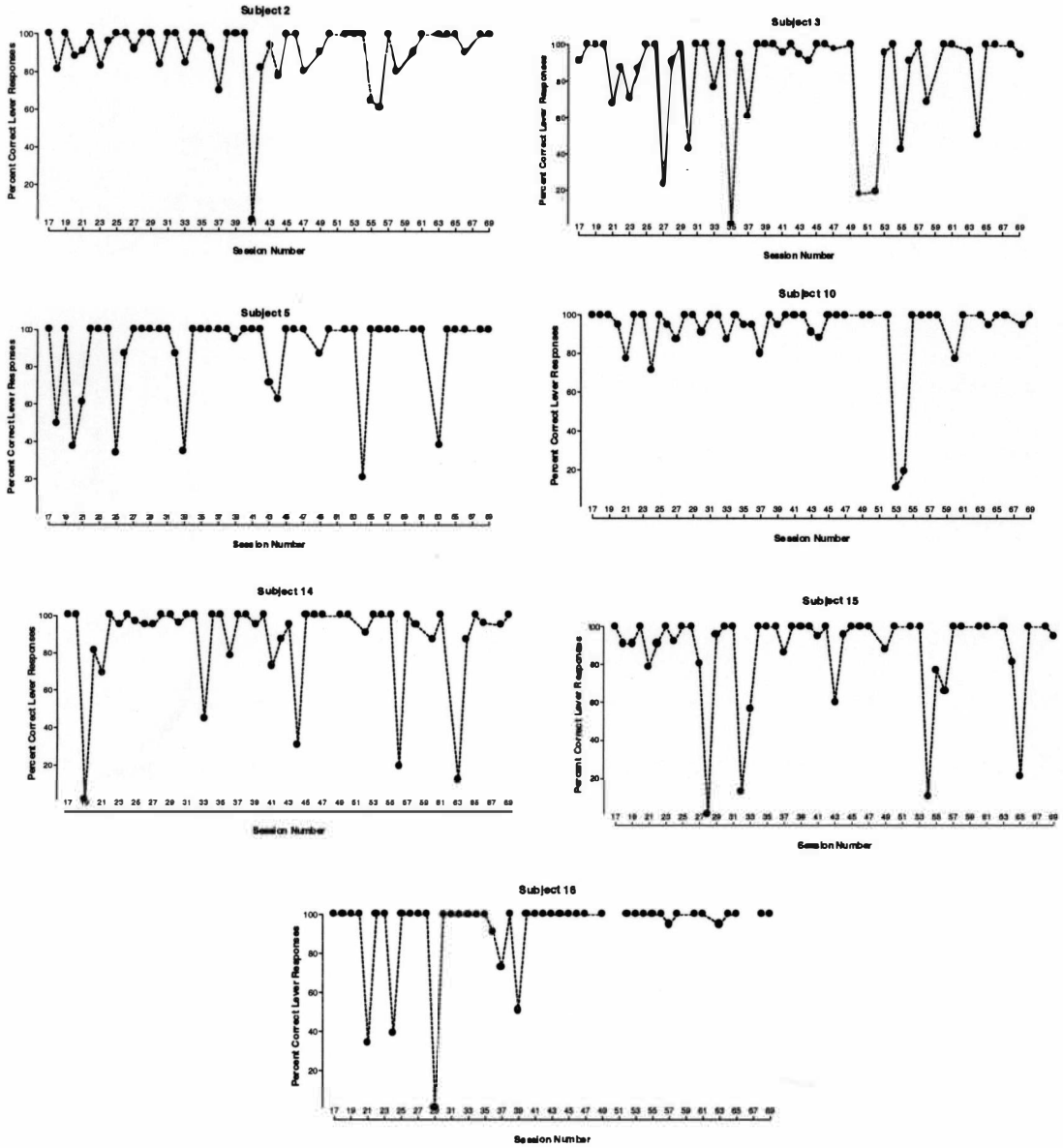


Figure 4. Individual Subject Data for Percent Correct First FR Across Training Sessions for the Saline Pretreated Group.

The latency to the first fixed ratio was examined, the means were collapsed over sessions. The MP pretreated group took longer than the saline pretreated group to successfully complete their first FR. The mean number of seconds to the first FR for the MP pretreated group is 571.1 ± 113.9 and the mean number of seconds for the saline pretreated group is 241.6 ± 78.01. Statistical analysis indicates that the means are significantly different ($t=2.39$, $df_{94}$, $p=0.01$, see Figure 5).

Concern regarding the use of reinforced trials during the cumulative dosing procedure motivated the implementation of a trial procedure. Our concern was that the animals would continue to respond on the lever that produced the reinforcer on the previous trial. This was not the case, as evident by the data presented in Figure 6. Sixteen rats were randomly divided into three groups. Each group received the training dose of cocaine at a different stage of the cumulative dose procedure. This was done to assure that accurate stimulus control was maintained during repeated dosing procedures.

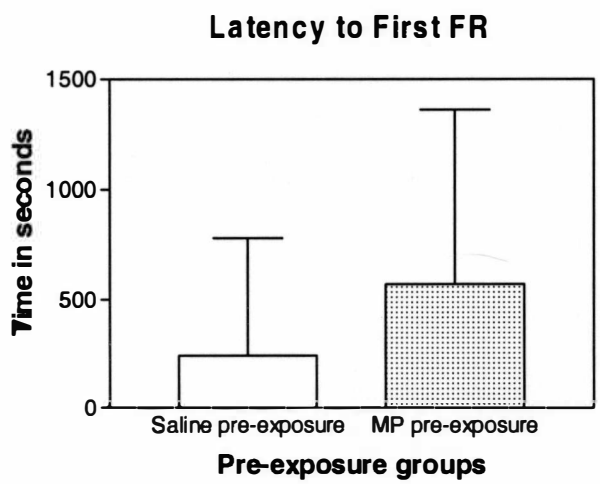


Figure 5. Results of Latency to First FR Between Groups.

Figure 6a illustrates the results of tests when cocaine was introduced in the second phase, 6b when cocaine was introduced in the third phase, and Figure 6c when cocaine was introduced in the fourth phase. In each case the subjects respond appropriately, switching from the saline- appropriate lever to the cocaine-appropriate lever when cocaine was introduced. The introduction of drug reliably produced greater than 80% responding on the drug appropriate lever. This trial procedure was conducted three times and subjects were systematically exposed to all three trial phases.

Following the determination that the commutative dosing procedure produced reliable results, training was resumed for two sessions, one saline treatment day and one cocaine treatment day. Cumulative dosing procedures were then implemented to conduct stimulus generalization tests with cocaine (0, 0.3, 1.0, 3.0, 10.0 mg/kg). Testing was first conducted after a drug training day (Figure 7), and then after a saline training day (Figure 8). The rate of responding was not significantly decreased in a dose-dependent fashion. There was a significant dose effect in both tests (Figure 7, $F = 8.59$, $df_{4, 50}$, $p < 0.0001$; Figure 8, $F = 8.52$, $df_{4, 47}$, $p<0.0001$). There was no significant effect of pre-exposure in the cocaine dose-response curve following cocaine training day ($F = 0.01$, $df_{1, 50}$, $p = 0.94$); nor was there a significant pretreatment effect on the cocaine dose-response curve following a saline training day ($F = 0.88$, $df_{1, 47}$, $p=0.35$). There was no significant interaction between dose and treatment in either dose response curve.

Methylphenidate substitution tests were conducted. Stimulus generalization with MP revealed similar dose response curves in both groups (Figure 9). Full substitution was apparent at doses of 4.0 mg/kg and 8.0

mg/kg in both groups. There was a significant dose-dependent decrease in response rate ($F=8.59$, $df_{4,50}$, $p<0.0001$) and there were no significant treatment effects on response rate ($F=0.01$, $df_{1,50}$, $p=0.94$) nor were there significant interaction effects ($F=0.57$, $df_{4,50}$, $p= 0.68$). The $ED_{50}$'s for the treatment groups were 2.22 mg/kg for the MP pretreated group and 2.0 mg/kg for the saline pretreated group.

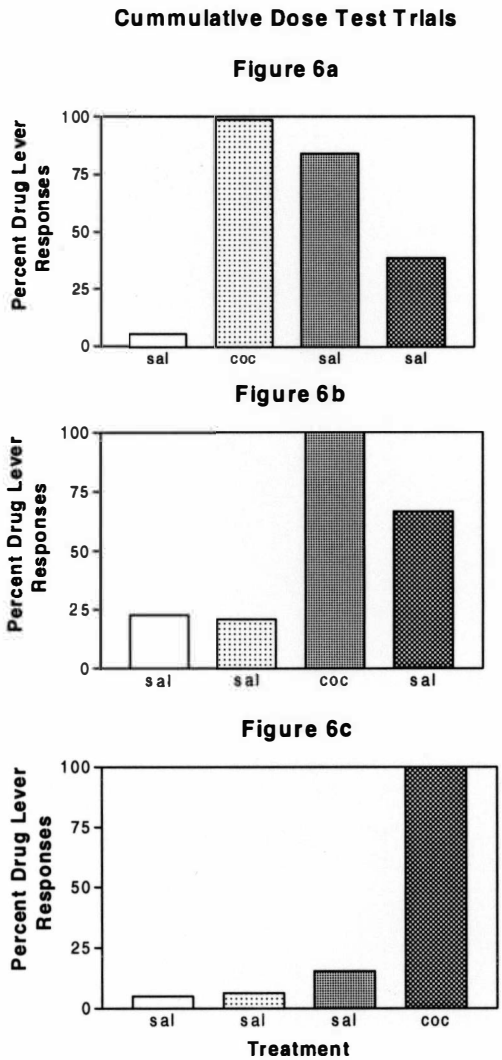


Figure 6. Results of the Cumulative Dosing Test Trials.

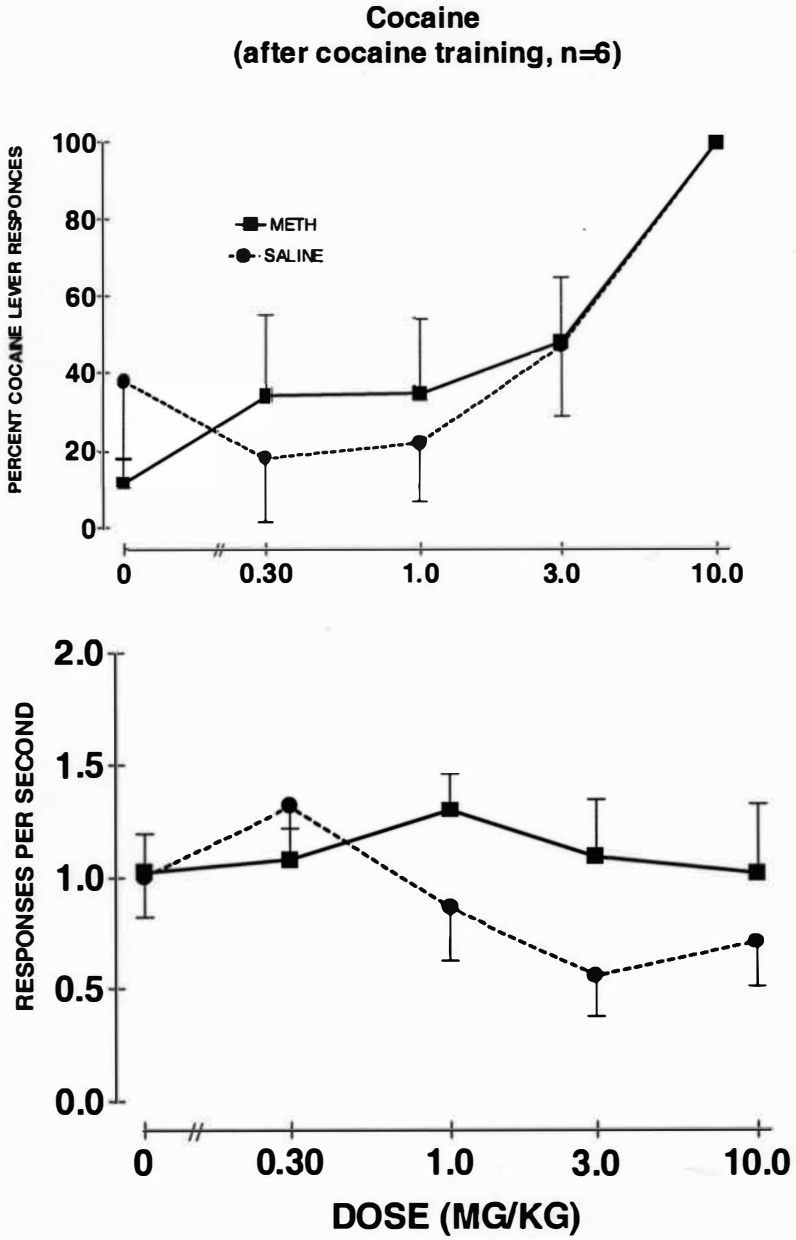


Figure 7. Results of Cocaine Dose-Response Tests Following a Cocaine Training Day.

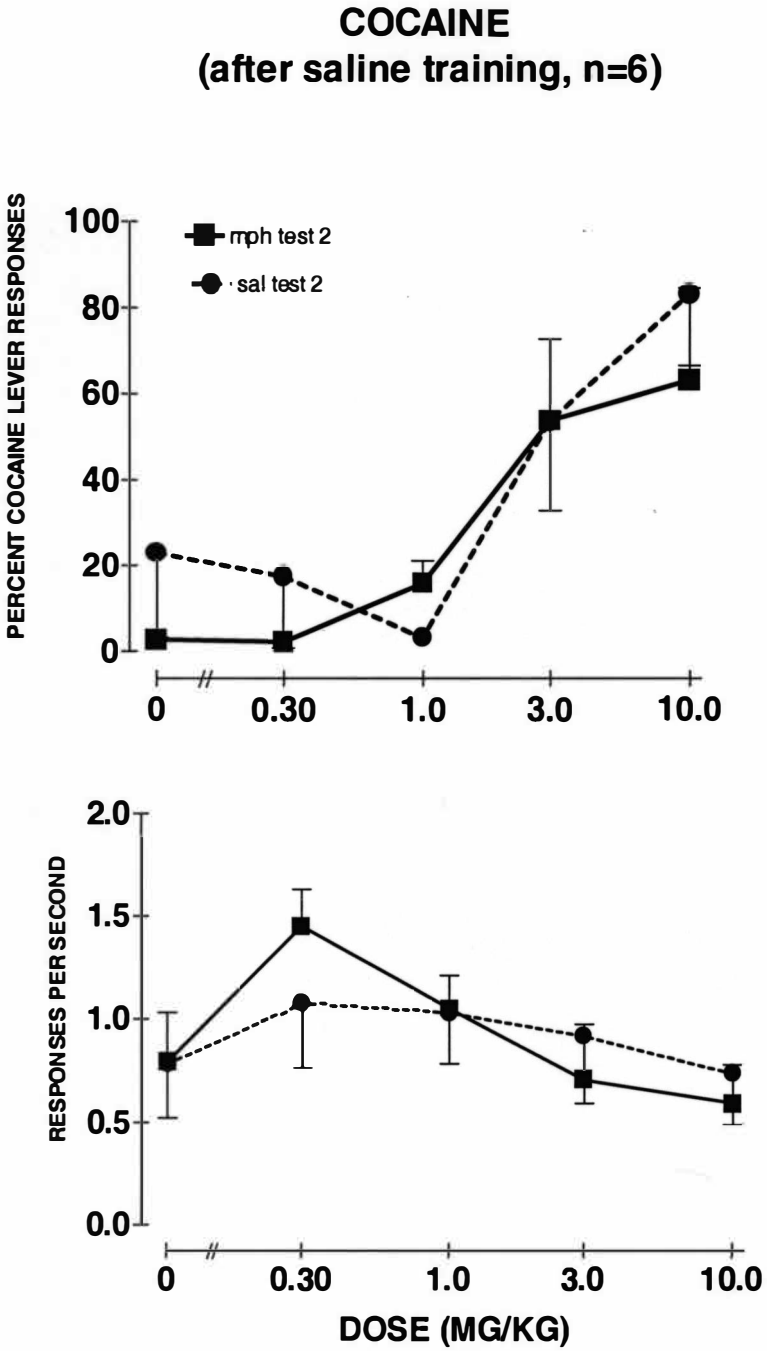


Figure 8. Results of Cocaine Dose-Response Test Following a Saline Training Day.

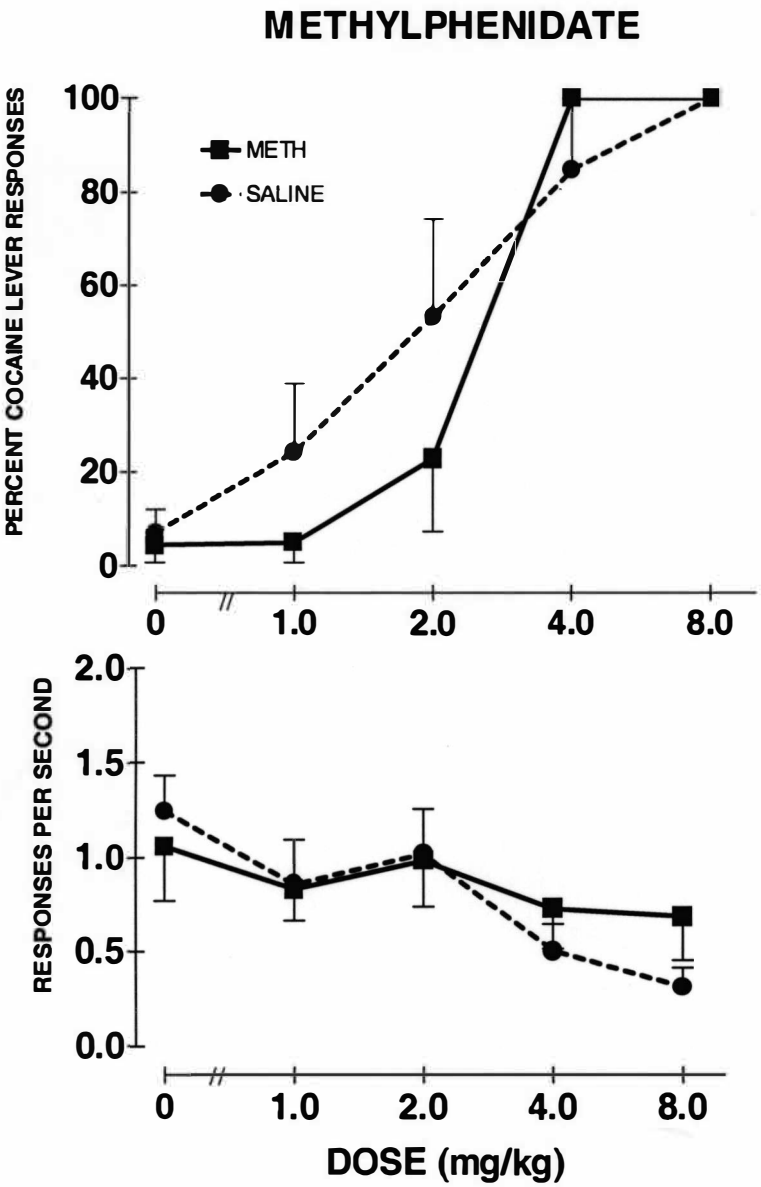


Figure 9. Result of the Methylphenidate Dose-Response Tests.

# DISCUSSION

The primary goal of the present study was to assess if methylphenidate would affect the stimulus properties of cocaine. Results indicate that exposure to 10 mg/kg methylphenidate for five consecutive days did not produce marked effects on the acquisition of a cocaine discrimination. There was no significant difference in the number of sessions to criterion between groups. This suggests that MP pretreatment did not significantly affect the acquisition of cocaine discrimination. In fact, contrary to the anticipated outcome, the MP pretreated group appeared slightly slower to acquire cocaine discrimination. In light of the fact that stimulant exposure is reported to enhance the acquisition of cocaine self-administration (Horger, Shelton and Schenk, 1990), this may suggest that the subjective effects of drugs require a more rigorous pretreatment period.

Although this trend was not statistically significant, all analyses in the present study support the theory that MP pretreated group tended to be less accurate than the saline pretreated group. The MP pretreated group express lower rates of accuracy, and significantly longer latencies to the first FR. A linear regression of first FR data across all training sessions indicates the MP treated animals exhibited lower terminal accuracy. The results of this study suggest that MP exposure may have effects on learning, however further investigation is needed to ascertain what those effects are. A continuation of the present study may examine the effects of a similar exposure procedure on a memory task such as maze learning.

Both treatment groups exhibited similar cocaine and methylphenidate dose-response functions. The MP pretreated group did not express an enhanced response to the low doses of cocaine nor did the exposure significantly shift the methylphenidate dose response function. Methylphenidate did fully substituted at doses of 4.0 mg/kg and 8.0 mg/kg for the training-dose (10 mg/kg) of cocaine. This is consistent with previous research indicating a similarity between the stimulus cues of methylphenidate and cocaine (Dackis and Gold, 1990; Volkow et al., 1995).

The secondary goal of this study was to examine the use of drug discrimination as a tool for studying sensitization. We established the ground work for examining drug discrimination as a tool for measuring effects of drug history on performance. Although the pretreatment did not significantly enhance the subjective drug experience, perhaps future investigations will examine the effects of chronic stimulant treatment on the dose-response function.

There were procedural issues that are inherent to the drug discrimination procedure, which made a between groups study difficult to tailor for individual subjects. Because MP treatment was the crucial variable in the study, all discrimination training had to be identical between groups for any reliable statement to be made regarding history. For such studies to be valid, it is essential that they hold constant the current environmental circumstances at the time. As noted in the results, two subjects required a reduced FR following the treatment. Therefore, they were not used in the analysis of sessions to criterion.

Another possible limitation of the drug discrimination assays is the

length of time it takes for subjects to achieve reliable responding. During the training period, subjects received the training drug, 10 mg/kg cocaine up to three days per week. It may be that the training procedures have an interactive effect with the pretreatment, diminishing the effect of the sensitization, and perhaps inducing tolerance.

The clinical relavance of this experiment is difficult to interpret. Since pretreatment did not affect the dose response function, it can be concluded that either the pretreatment did not produce adequate sensitization to shift the curve to the left, or that sensitization does not enhance the subjective effects of cocaine. A follow-up study might increase the duration of the pretreatment phase, and test for cross-sensitization to the locomotor effects of cocaine prior to the discrimination training.

# Appendix A

## Protocol Clearance From the Institutional Animal Care and Use Committee (IACUC)

**WESTERN MICHIGAN UNIVERSITY**
**INVESTIGATOR IACUC CERTIFICATE**

Title of Project: Assessment of Methylphenidate Sensitization Using a Drug Discrimination Procedure

The information included in this IACUC application is accurate to the best of my knowledge. All personnel listed recognize their responsibility in complying with university policies governing the care and use of animals.

I declare that all experiments involving live animals will be performed under my supervision or that of another qualified scientist. Technicians or students involved have been trained in proper procedures in animal handling, administration of anesthetics, analgesics, and euthanasia to be used in this project.

If this project is funded by an extramural source, I certify that this application accurately reflects all procedures involving laboratory animal subjects described in the proposal to the funding agency noted above.

Any proposed revisions to or variations from the animal care and use data will be promptly forwarded to the IACUC for approval.

_____ Disapproved _____ Approved X Approved with the provisions listed below

Provisions or Explanations:
State that Animal Facilities (not basement) will be used.
Please give maximum amount of time animals will be in testing chambe-
- NEED ORIGINAL SIGNATURES (NOT COPY) ON PAGE 1 OF PROTOCOL FORM FOR FILES. ADDED 4/2/99

IACUC Chairperson — Date 5/29/99

Acceptance of Provisions

Signature: Principal Investigator/Instructor — Date 4/14/99

IACUC Chairperson Final Approval — Date 4/28/99
Approved IACUC Number 99-02-02

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